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     (FILE 'HOME' ENTERED AT 12:01:16 ON 21 JAN 2005)

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L1             0 S SODIUM NEAR CHANNEL
L2             0 S SODIUM ADJ CHANNEL
L3         11547 S SODIUM CHANNEL
L4          1582 S L3 AND (MUTANT OR MUTANTS OR MUTATION)
L5             3 S L4 AND NAV
L6            44 S L4 AND NAV!
L7             0 S L6 AND SCREEN
L8             1 S L6 AND METHOD
L9             0 S L6 AND ARRHYTHMIC
L10            0 S L6 (S) ARRHYTHMIC
L11            8 S L6 AND PY<2003

     FILE 'CAPLUS, MEDLINE, BIOSIS, USPATFULL' ENTERED AT 12:07:31 ON 21 JAN
     2005
L12           87 S L11
L13           62 DUP REM L12 (25 DUPLICATES REMOVED)
L14           14 S L13 AND METHOD
L15           27 S L13 AND PY<2002
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L15 ANSWER 1 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
TI Identification of an axonal determinant in the C-terminus of the **sodium channel Nav1**.2
PY **2001**
AU Garrido, Juan Jose; Fernandes, Fanny; Giraud, Pierre; Mouret, Isabelle; Pasqualini, Eric; Fache, Marie-Pierre; Jullien, Florence; Dargent, Benedicte
SO EMBO Journal (**2001**), 20(21), 5950-5961
CODEN: EMJODG; ISSN: 0261-4189
TI Identification of an axonal determinant in the C-terminus of the **sodium channel Nav1**.2
SO EMBO Journal (**2001**), 20(21), 5950-5961
CODEN: EMJODG; ISSN: 0261-4189
AB . . . of how hippocampal neurons selectively target proteins to axons, we assessed whether any of the large cytoplasmic regions of neuronal **sodium channel Nav1**.2 contain sufficient information for axonal compartmentalization. We show that addition of the cytoplasmic C-terminal region of **Nav1**.2 restricted the distribution of a dendritic-axonal reporter protein to axons. The anal. of **mutants** revealed that a critical segment of nine amino acids encompassing a di-leucine-based motif mediates axonal compartmentalization of chimera. In addition, the **Nav1**.2 C-terminus is recognized by the clathrin endocytic pathway both in non-neuronal cells and the somato-dendritic domain of hippocampal neurons. The **mutation** of the di-leucine motif located within the nine amino acid sequence to alanines resulted in the loss of chimera compartmentalization. . .
ST Nav12 **sodium channel** clathrin endocytosis axon hippocampus
IT Clathrin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(C-terminus of **sodium channel Nav1**.2 is recognized by clathrin endocytic pathway)
IT **Sodium channel**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(**Nav1**.2; identification of axonal determinant in C-terminus of **sodium channel Nav1**.2)
IT Protein motifs
(di-leucine; identification of axonal determinant in C-terminus of **sodium channel Nav1**.2)
IT Brain
(hippocampus; identification of hippocampal axonal determinant in C-terminus of **sodium channel Nav1**.2)
IT Axon
(identification of axonal determinant in C-terminus of **sodium channel Nav1**.2)
IT Endocytosis
(receptor-mediated; C-terminus of **sodium channel Nav1**.2 is recognized by clathrin endocytic pathway)

L15 ANSWER 2 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
TI Functional effects of two voltage-gated **sodium channel mutations** that cause generalized epilepsy with febrile seizures plus type 2
PY **2001**
AU Spampanato, Jay; Escayg, Andrew; Meisler, Miriam H.; Goldin, Alan L.
SO Journal of Neuroscience (**2001**), 21(19), 7481-7490
CODEN: JNRSDS; ISSN: 0270-6474
TI Functional effects of two voltage-gated **sodium channel mutations** that cause generalized epilepsy with febrile seizures plus type 2

SO Journal of Neuroscience (**2001**), 21(19), 7481-7490
CODEN: JNRSDS; ISSN: 0270-6474

AB Two **mutations** that cause generalized epilepsy with febrile seizures plus (GEFS+) have been identified previously in the SCN1A gene encoding the α subunit of the **Nav1**.1 voltage-gated **sodium channel**. Both **mutations** change conserved residues in putative voltage-sensing S4 segments, T875M in domain II and R1648H in domain IV. Each **mutation** was cloned into the orthologous rat channel rNav1.1, and the properties of the **mutant** channels were determined in the absence and presence of the β1 subunit in Xenopus oocytes. Neither **mutation** significantly altered the voltage dependence of either activation or inactivation in the presence of the β1 subunit. The most prominent effect of the T875M **mutation** was to enhance slow inactivation in the presence of β1, with small effects on the kinetics of recovery from inactivation. . . of the channel in both the presence and absence of the β1 subunit. The most prominent effects of the R1648H **mutation** were to accelerate recovery from inactivation and decrease the use dependence of channel activity with and without the β1 subunit. The DIV **mutation** would cause a phenotype of **sodium channel** hyperexcitability, whereas the DII **mutation** would cause a phenotype of **sodium channel** hypoexcitability, suggesting that either an increase or decrease in **sodium channel** activity can result in seizures.

ST **sodium channel** transport SCN1A gene **mutation** epilepsy febrile seizure

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(SCN1A; functional effects of two voltage-gated **sodium channel mutations** that cause generalized epilepsy with febrile seizures plus type 2)

IT Electric potential
(biol., action; functional effects of two voltage-gated **sodium channel mutations** that cause generalized epilepsy with febrile seizures plus type 2)

IT Biological transport
(channel-mediated; functional effects of two voltage-gated **sodium channel mutations** that cause generalized epilepsy with febrile seizures plus type 2)

IT Polarization
(depolarization, biol.; functional effects of two voltage-gated **sodium channel mutations** that cause generalized epilepsy with febrile seizures plus type 2)

IT Fever and Hyperthermia
Seizures
(functional effects of two voltage-gated **sodium channel mutations** that cause generalized epilepsy with febrile seizures plus type 2)

IT Epilepsy
(genetic; functional effects of two voltage-gated **sodium channel mutations** that cause generalized epilepsy with febrile seizures plus type 2)

IT **Mutation**
(substitution, T875M and R1648H; functional effects of two voltage-gated **sodium channel mutations** that cause generalized epilepsy with febrile seizures plus type 2)

IT **Sodium channel**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(voltage-gated, α-subunit; functional effects of two

voltage-gated **sodium channel mutations**
that cause generalized epilepsy with febrile seizures plus type 2)

IT 7440-23-5, Sodium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transport; functional effects of two voltage-gated **sodium channel mutations** that cause generalized epilepsy with febrile seizures plus type 2)

L15 ANSWER 3 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
TI A missense **mutation** of the Na+ channel αII subunit gene **Nav1**.2 in a patient with febrile and afebrile seizures causes channel dysfunction. [Erratum to document cited in CA135:120662]
PY **2001**
AU Sugawara, Takashi; Tsurubuchi, Yuji; Agarwala, Kishan Lal; Ito, Masatoshi; Fukuma, Goryu; Mazaki-Miyazaki, Emi; Nagafuji, Hiroshi; Noda, Masaharu; Imoto, Keiji; Wada, Kazumaru; Mitsudome, Akihisa; Kaneko, Sunao; Montal, Mauricio; Nagata, Keiichi; Hirose, Shinichi; Yamakawa, Kazuhiro
SO Proceedings of the National Academy of Sciences of the United States of America (**2001**), 98(18), 10515
CODEN: PNASA6; ISSN: 0027-8424
TI A missense **mutation** of the Na+ channel αII subunit gene **Nav1**.2 in a patient with febrile and afebrile seizures causes channel dysfunction. [Erratum to document cited in CA135:120662]
SO Proceedings of the National Academy of Sciences of the United States of America (**2001**), 98(18), 10515
CODEN: PNASA6; ISSN: 0027-8424
AB The position given for the amino acid that was mutated in the patient was incorrect; the **mutation** "R187W" should be "R188W".
ST erratum **sodium channel** gene **mutation** febrile seizure epilepsy; **sodium channel** gene **mutation** febrile seizure epilepsy erratum
IT Epilepsy
Genetic inheritance
Human
Susceptibility (genetic)
(Na+ channel αII subunit gene **Nav1**.2 missense **mutations** in human febrile and afebrile seizures causes channel dysfunction (Erratum))
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(Na+ channel αII subunit gene **Nav1**.2 missense **mutations** in human febrile and afebrile seizures causes channel dysfunction (Erratum))
IT Electric properties
(biol.; Na+ channel αII subunit gene **Nav1**.2 missense **mutations** in human febrile and afebrile seizures causes channel dysfunction (Erratum))
IT Seizures
(febrile; Na+ channel αII subunit gene **Nav1**.2 missense **mutations** in human febrile and afebrile seizures causes channel dysfunction (Erratum))
IT **Mutation**
(missense; Na+ channel αII subunit gene **Nav1**.2 missense **mutations** in human febrile and afebrile seizures causes channel dysfunction (Erratum))
IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(type II; Na+ channel αII subunit gene **Nav1**.2 missense **mutations** in human febrile and afebrile seizures causes channel dysfunction (Erratum))

L15 ANSWER 4 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
TI **Nav1**.1 **mutations** cause febrile seizures associated with afebrile partial seizures
PY **2001**
AU Sugawara, T.; Mazaki-Miyazaki, E.; Ito, M.; Nagafuji, H.; Fukuma, G.; Mitsudome, A.; Wada, K.; Kaneko, S.; Hirose, S.; Yamakawa, K.
SO Neurology (**2001**), 57(4), 703-705
CODEN: NEURAI; ISSN: 0028-3878
TI **Nav1**.1 **mutations** cause febrile seizures associated with afebrile partial seizures
SO Neurology (**2001**), 57(4), 703-705
CODEN: NEURAI; ISSN: 0028-3878
AB Recent evidence has suggested that the neuronal voltage-gated **sodium channel** α1-subunit gene (**Nav1**.1: SCN1A) is responsible for generalized epilepsy with febrile seizures plus (GEFS+2). Here the authors report two novel disease **mutations** of **Nav1**.1 in patients with febrile seizures associated with afebrile partial seizures. One is a Val1428Ala substitution in the pore-forming region, and. . .
ST **sodium channel mutation** febrile seizure epilepsy
IT Human
Seizures
(**Nav1**.1 **mutations** cause febrile seizures associated with afebrile partial seizures)
IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); PRP (Properties); BIOL (Biological study)
(**Nav1**.1 **mutations** cause febrile seizures associated with afebrile partial seizures)
IT Epilepsy
(generalized epilepsy with febrile seizures plus; **Nav1**.1 **mutations** cause febrile seizures associated with afebrile partial seizures)
IT **Mutation**
(missense, V1428A and A1685V; **Nav1**.1 **mutations** cause febrile seizures associated with afebrile partial seizures)

L15 ANSWER 5 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
TI A phenylalanine residue at segment D3-S6 in **Nav1**.4 voltage-gated Na+ channels is critical for pyrethroid action
PY **2001**
AU Wang, Sho-Ya; Barile, Maria; Wang, Ging Kuo
SO Molecular Pharmacology (**2001**), 60(3), 620-628
CODEN: MOPMA3; ISSN: 0026-895X
TI A phenylalanine residue at segment D3-S6 in **Nav1**.4 voltage-gated Na+ channels is critical for pyrethroid action
SO Molecular Pharmacology (**2001**), 60(3), 620-628
CODEN: MOPMA3; ISSN: 0026-895X
AB . . . to 3 orders of magnitude. Deltamethrin at 10 μM elicited weak gating changes in rat skeletal muscle α-subunit Na+ channels (**Nav1**.4) after > 30 min of perfusion. About 10% of the peak current was maintained during the 8-ms, +50-mV pulse and,. . . amplitude of the slow tail current corresponded to less than 3% of total Na+ channels modified by deltamethrin. A background **mutation**, **Nav1**.4-I687M (within D2:S4-S5 cytoplasmic linker), enhanced the deltamethrin-induced maintained current by .apprx.2.5-fold, whereas **Nav1**.4-I687T, a homologous superkdr **mutation**, reduced it by .apprx.2-fold. Repetitive pulses at 2 Hz further augmented the effects of deltamethrin on **Nav1**.4-I687M **mutant** channels so that .apprx.75% of peak currents were maintained. A second

mutation, Navl.4-I687M/F1278I at the middle of D3-S6, rendered the channel greatly resistant to deltamethrin. This double **mutant** channel remained sensitive to batrachotoxin (BTX), even though nearby residues S1276 and L1280 were critical for BTX action. We hypothesize. . . deltamethrin receptor and the BTX receptor are situated at the middle but opposite surface of the D3-S6 α-helical structure. Another **mutant, Navl**.4-I687M/N784K, exhibited a partial deltamethrin-resistant phenotype but was completely resistant to BTX. Consistent with the BTX-resistant phenotype of N784K and the known adjacent kdr **mutation** at position L785F, deltamethrin and BTX were probably situated next to each other upon binding at D2-S6. Evidently, distinct residues. . .

ST phenylalanine **sodium channel** deltamethrin muscle toxicity

IT Animal cell line
(HEK293t; phenylalanine residue at segment D3-S6 in **Navl**.4 voltage-gated Na+ channels is critical for pyrethroid action)

IT Receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(batrachotoxin; phenylalanine residue at segment D3-S6 in **Navl**.4 voltage-gated Na+ channels is critical for pyrethroid action)

IT Protein sequences
(phenylalanine residue at segment D3-S6 in **Navl**.4 voltage-gated Na+ channels is critical for pyrethroid action)

IT **Sodium channel**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(phenylalanine residue at segment D3-S6 in **Navl**.4 voltage-gated Na+ channels is critical for pyrethroid action)

IT 23509-16-2, Batrachotoxin 52918-63-5, Deltamethrin
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(phenylalanine residue at segment D3-S6 in **Navl**.4 voltage-gated Na+ channels is critical for pyrethroid action)

IT 63-91-2, Phenylalanine, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(phenylalanine residue at segment D3-S6 in **Navl**.4 voltage-gated Na+ channels is critical for pyrethroid action)

L15 ANSWER 6 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN

TI A missense **mutation** of the Na+ channel αII subunit gene **Navl**.2 in a patient with febrile and afebrile seizures causes channel dysfunction

PY **2001**

AU Sugawara, Takashi; Tsurubuchi, Yuji; Agarwala, Kishan Lal; Ito, Masatoshi; Fukuma, Goryu; Mazaki-Miyazaki, Emi; Nagafuji, Hiroshi; Noda, Masaharu; Imoto, Keiji; Wada, Kazumaru; Mitsudome, Akihisa; Kaneko, Sunao; Montal, Mauricio; Nagata, Keiichi; Hirose, Shinichi; Yamakawa, Kazuhiro

SO Proceedings of the National Academy of Sciences of the United States of America (**2001**), 98(11), 6384-6389
CODEN: PNASA6; ISSN: 0027-8424

TI A missense **mutation** of the Na+ channel αII subunit gene **Navl**.2 in a patient with febrile and afebrile seizures causes channel dysfunction

SO Proceedings of the National Academy of Sciences of the United States of America (**2001**), 98(11), 6384-6389
CODEN: PNASA6; ISSN: 0027-8424

AB . . . febrile seizures (FS), is characterized by frequent episodes beyond 6 yr of age (FS+) and various types of subsequent epilepsy. **Mutations** in β1 and α1-subunit genes of voltage-gated Na+ channels have been associated with GEFS+1 and 2, resp. Here, we report a

mutation resulting in an amino acid exchange (R187W) in the gene encoding the α-subunit of neuronal voltage-gated Na+ channel type II (**Nav1**.2) in a patient with FS associated with afebrile seizures. The **mutation** R187W occurring on Arg187, a highly conserved residue among voltage-gated Na+ channels, was not found in 224 alleles of unaffected individuals. Whole-cell patch clamp recordings on human embryonic kidney (HEK) cells expressing a rat wild-type (rNav1.2) and the corresponding **mutant** channels showed that the **mutant** channel inactivated more slowly than wild-type whereas the Na+ channel conductance was not affected. Prolonged residence in the open state of the R187W **mutant** channel may augment Na+ influx and thereby underlie the neuronal hyperexcitability that induces seizure activity. Even though a small pedigree could not show clear cosegregation with the disease phenotype, these findings strongly suggest the involvement of **Nav1**.2 in a human disease and propose the R187W **mutation** as the genetic defect responsible for febrile seizures associated with afebrile seizures.

ST **sodium channel** gene **mutation** febrile seizure epilepsy

IT Epilepsy
Genetic inheritance
Susceptibility (genetic)
(Na+ channel αII subunit gene **Nav1**.2 missense **mutations** in human febrile and afebrile seizures causes channel dysfunction)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(Na+ channel αII subunit gene **Nav1**.2 missense **mutations** in human febrile and afebrile seizures causes channel dysfunction)

IT Electric properties
(biol.; Na+ channel αII subunit gene **Nav1**.2 missense **mutations** in human febrile and afebrile seizures causes channel dysfunction)

IT Seizures
(febrile; Na+ channel αII subunit gene **Nav1**.2 missense **mutations** in human febrile and afebrile seizures causes channel dysfunction)

IT **Mutation**
(missense; Na+ channel αII subunit gene **Nav1**.2 missense **mutations** in human febrile and afebrile seizures causes channel dysfunction)

IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(type II; Na+ channel αII subunit gene **Nav1**.2 missense **mutations** in human febrile and afebrile seizures causes channel dysfunction)

L15 ANSWER 7 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN

TI D1/D5 dopamine receptor activation differentially modulates rapidly inactivating and persistent sodium currents in prefrontal cortex pyramidal neurons

PY **2001**

AU Maurice, Nicolas; Tkatch, Tatiana; Meisler, Miriam; Sprunger, Leslie K.; Surmeier, D. James

SO Journal of Neuroscience (**2001**), 21(7), 2268-2277
CODEN: JNRSDS; ISSN: 0270-6474

SO Journal of Neuroscience (**2001**), 21(7), 2268-2277

CODEN: JNRSDS; ISSN: 0270-6474

AB . . . persistent Na+ currents arise in part from different channels. Single-cell RT-PCR profiling showed that pyramidal neurons coexpressed three α-subunit mRNAs (**Nav1**.1, 1.2, and 1.6) that code for the Na+ channel pore. In neurons from **Nav1**.6 null mice the persistent Na+ currents were significantly smaller than in wild-type neurons. Moreover, the residual persistent currents in these **mutant** neurons-which are attributable to **Nav1**.1/1.2 channels-were reduced significantly by PKA activation. These results argue that D1/D5 DA receptor activation reduces the rapidly inactivating component of Na+ current in PFC pyramidal neurons arising from **Nav1**.1/1.2 Na+ channels but does not modulate effectively the persistent component of the Na+ current that is attributable to **Nav1**.6 Na+ channels.

IT **Sodium channel**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**Nav1**.1; D1 and D5 dopamine receptors activation differentially modulates rapidly inactivating and persistent sodium currents in prefrontal cortex pyramidal neurons)

IT **Sodium channel**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**Nav1**.6; D1 and D5 dopamine receptors activation differentially modulates rapidly inactivating and persistent sodium currents in prefrontal cortex pyramidal neurons)

IT **Sodium channel**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**sodium channel**; D1 and D5 dopamine receptors activation differentially modulates rapidly inactivating and persistent sodium currents in prefrontal cortex pyramidal neurons)

IT mRNA
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(**sodium channels**; D1 and D5 dopamine receptors activation differentially modulates rapidly inactivating and persistent sodium currents in prefrontal cortex pyramidal neurons)

L15 ANSWER 8 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN

TI The intracellular segment of the **sodium channel** β1 subunit is required for its efficient association with the channel α subunit

PY **2001**

AU Meadows, Laurence; Malhotra, Jyoti Dhar; Stetzer, Alisa; Isom, Lori L.; Ragsdale, David S.

SO Journal of Neurochemistry (**2001**), 76(6), 1871-1878
CODEN: JONRA9; ISSN: 0022-3042

TI The intracellular segment of the **sodium channel** β1 subunit is required for its efficient association with the channel α subunit

SO Journal of Neurochemistry (**2001**), 76(6), 1871-1878
CODEN: JONRA9; ISSN: 0022-3042

AB **Sodium channels** consist of a pore-forming α subunit and auxiliary β1 and β2 subunits. The subunit β1 alters the kinetics and voltage-dependence of **sodium channels** expressed in Xenopus oocytes or mammalian cells. Functional modulation in oocytes depends on specific regions in the N-terminal extracellular domain. . . and thus could involve different

mol. mechanisms. As a first step toward testing this hypothesis, we examined modulation of brain **Nav1**.2a **sodium channel** α subunits expressed in Chinese hamster lung cells by a **mutant** β1 construct with 34 amino acids deleted from the C-terminus. This deletion **mutation** did not modulate **sodium channel** function in this cell system. Co-immunopptn. data suggest that this loss of functional modulation was caused by inefficient association of the **mutant** β1 with α, despite high levels of expression of the **mutant** protein. In Xenopus oocytes, injection of approx. 10 000 times more **mutant** β1 RNA was required to achieve the level of functional modulation observed with injection of full-length β1. Together, these findings suggest that the C-terminal cytoplasmic domain of β1 is an important determinant of β1 binding to the **sodium channel** α subunit in both mammalian cells and Xenopus oocytes.

ST **sodium channel** beta1 alpha subunit brain

IT Protein motifs
(cytoplasmic domain; role of C-terminal cytoplasmic domain of β1 subunit of brain **sodium channel** in β1-α subunit interaction)

IT Brain
(role of C-terminal cytoplasmic domain of β1 subunit of brain **sodium channel** in β1-α subunit interaction)

IT **Sodium channel**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(role of C-terminal cytoplasmic domain of β1 subunit of brain **sodium channel** in β1-α subunit interaction)

IT Biological transport
(sodium; role of C-terminal cytoplasmic domain of β1 subunit of brain **sodium channel** in β1-α subunit interaction)

IT 7440-23-5, Sodium, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(transport; role of C-terminal cytoplasmic domain of β1 subunit of brain **sodium channel** in β1-α subunit interaction)

L15 ANSWER 9 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN

TI Involvement of Na+ channels in pain pathways

PY **2001**

AU Baker, M. D.; Wood, J. N.

SO Trends in Pharmacological Sciences (**2001**), 22(1), 27-31
CODEN: TPHSDY; ISSN: 0165-6147

SO Trends in Pharmacological Sciences (**2001**), 22(1), 27-31
CODEN: TPHSDY; ISSN: 0165-6147

AB . . . changes in both channel expression and function are caused by disease. Recent evidence implicates specific roles for Na+ channel subtypes **Nav1**.3 and **Nav1**.8 in pain states that are associated with nerve injury and inflammation, resp. Insight into the role of **Nav1**.8 in pain pathways has been gained by the generation of a null **mutant**. Although drugs discriminate poorly between subtypes, the mol. diversity of channels and subtype-specific modulation might provide opportunities to target pain. . .

ST review **sodium channel** pain anesthesia

IT **Sodium channel**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(Na+ channels in pain pathways)

L15 ANSWER 10 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
TI A gain-of-function **mutation** in the **sodium channel** gene Scn2a results in seizures and behavioral abnormalities
PY **2001**
AU Kearney, J. A.; Plummer, N. W.; Smith, M. R.; Kapur, J.; Cummins, T. R.; Waxman, S. G.; Goldin, A. L.; Meisler, M. H.
SO Neuroscience (Oxford, United Kingdom) (**2001**), 102(2), 307-317
CODEN: NRSCDN; ISSN: 0306-4522
TI A gain-of-function **mutation** in the **sodium channel** gene Scn2a results in seizures and behavioral abnormalities
SO Neuroscience (Oxford, United Kingdom) (**2001**), 102(2), 307-317
CODEN: NRSCDN; ISSN: 0306-4522
AB The GAL879-881QQQ **mutation** in the cytoplasmic S4-S5 linker of domain 2 of the rat brain IIA **sodium channel** (**Nav1**.2) results in slowed inactivation and increased persistent current when expressed in Xenopus oocytes. The neuron-specific enolase promoter was used to. . . shortened and only 25% of the mice survived beyond six months of age. Four independent transgenic lines expressing the wild-type **sodium channel** were examined and did not exhibit any abnormalities. The transgenic Q54 mice provide a genetic model that will be useful for testing the effect of pharmacol. intervention on progression of seizures caused by **sodium channel** dysfunction. The human ortholog, SCN2A, is a candidate gene for seizure disorders mapped to chromosome 2q22-24.
ST gene Scn2a **sodium channel mutation** seizure behavioral abnormality
IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
(Scn2a; gain-of-function **mutation** in rat **sodium channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)
IT Transgene
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
(animal; gain-of-function **mutation** in rat **sodium channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice in relation to)
IT Brain
(cerebral cortex; gain-of-function **mutation** in rat **sodium channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice in relation to)
IT Behavior
(disorder; gain-of-function **mutation** in rat **sodium channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)
IT Protein motifs
(domain 2 S4-S5 linker; gain-of-function **mutation** in rat **sodium channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)
IT Brain
Disease models
Mouse
Mutation
Rat

Seizures
(gain-of-function **mutation** in rat **sodium** **channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)

IT Death
Development, mammalian postnatal
(gain-of-function **mutation** in rat **sodium** **channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice in relation to)

IT **Sodium channel**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(gene Scn2a; gain-of-function **mutation** in rat **sodium** **channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)

IT Neuroglia
(gliosis; gain-of-function **mutation** in rat **sodium** **channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)

IT Brain
(hippocampus, hilus; gain-of-function **mutation** in rat **sodium channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)

IT Brain
(hippocampus, sector CA1; gain-of-function **mutation** in rat **sodium channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)

IT Brain
(hippocampus, sector CA2; gain-of-function **mutation** in rat **sodium channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)

IT Brain
(hippocampus, sector CA3; gain-of-function **mutation** in rat **sodium channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)

IT Electric current
(ionic, biol.; gain-of-function **mutation** in rat **sodium channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)

IT Nerve
(neuron; gain-of-function **mutation** in rat **sodium** **channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)

IT 7440-23-5, Sodium, biological studies
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(channel and current; gain-of-function **mutation** in rat **sodium channel** gene Scn2a results in seizures and behavioral abnormalities in transgenic mice)

L15 ANSWER 11 OF 27 CAPLUS COPYRIGHT 2005 ACS on STN
TI **Nav2**/NaG channel is involved in control of salt-intake behavior in the CNS
PY **2000**
AU Watanabe, Eiji; Fujikawa, Akihiro; Matsunaga, Haruyuki; Yasoshima, Yasunobu; Sako, Noritaka; Yamamoto, Takashi; Saegusa, Chika; Noda, Masaharu
TI **Nav2**/NaG channel is involved in control of salt-intake behavior in the CNS
SO Journal of Neuroscience (**2000**), 20(20), 7743-7751
CODEN: JNRSDS; ISSN: 0270-6474
AB **Nav2**/NaG is a putative **sodium channel**, whose physiol. role has long been an enigma. We generated **Nav2** gene-deficient mice by inserting the lacZ gene. Anal. of the targeted mice allowed us to identify **Nav2**-producing cells by examining the lacZ expression. Besides in the lung, heart, dorsal root ganglia, and Schwann cells in the peripheral nervous system, **Nav2** was expressed in neurons and ependymal cells in restricted areas of the CNS, particularly in the circumventricular organs, which are. . . neurons in the subfornical organ and organum vasculosum laminae terminalis compared with wild-type animals, suggesting a hyperactive state in the **Nav2** -null mice. Moreover, the null **mutants** showed abnormal intakes of hypertonic saline under both water- and salt-depleted conditions. These findings suggest that the **Nav2** channel plays an important role in the central sensing of body-fluid sodium level and regulation of salt intake behavior.
ST **Nav2 sodium channel** DNA sequence circumventricular organ salt appetite
IT Animal tissue
DNA sequences
Mouse
Protein sequences
(**Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)
IT Thirst
(**Nav2**/NaG channel involvement in control of salt-intake behavior in CNS in relation to)
IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(**Nav2**; **Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)
IT Nervous system
(central; **Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)
IT Brain
(circumventricular organ; **Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)
IT Nerve
(neuron; **Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)
IT Brain
(organum vasculosum lamina terminalis; **Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)
IT Sensory receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(osmoreceptors; **Nav2**/NaG channel involvement in control of salt-intake behavior in CNS in relation to)
IT Behavior
(salt-intake; **Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)

IT Appetite
(salt; **Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)
IT Brain
(subfornical organ; **Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)
IT **Sodium channel**
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(voltage-gated; **Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)
IT 7647-14-5, Sodium chloride, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)
IT 308312-10-9
RL: BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(amino acid sequence; **Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)
IT 248228-40-2, GenBank AF190472
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(nucleotide sequence; **Nav2**/NaG channel involvement in control of salt-intake behavior in CNS)

L15 ANSWER 12 OF 27 MEDLINE on STN
TI Point **mutations** in homology domain II modify the sensitivity of rat **Nav1**.8 **sodium channels** to the pyrethroid insecticide cismethrin.
PY 2001
AU Soderlun D M; Lee S H
TI Point **mutations** in homology domain II modify the sensitivity of rat **Nav1**.8 **sodium channels** to the pyrethroid insecticide cismethrin.
SO Neurotoxicology, **(2001 Dec)** 22 (6) 755-65.
Journal code: 7905589. ISSN: 0161-813X.
AB Two point **mutations** in homology domain II of the housefly Vsscl voltage-sensitive **sodium channel** subunit, M918T and L1014F are associated with resistance to pyrethroid insecticides and reduce the pyrethroid sensitivity of Vsscl **sodium channels** expressed in Xenopus laevis oocytes. To assess the impact of these residues as determinants of pyrethroid sensitivity in another sequence context, we mutated the corresponding positions of the rat pyrethroid-sensitive, TTX-resistant peripheral nerve **sodium channel** (rNav1.8; also called SNS or PN3) and determined the sensitivity of native and mutated channels expressed in Xenopus oocytes to the pyrethroid insecticide cismethrin. The rNav1.8 channel, like other vertebrate **sodium channel** isoforms, contains a conserved isoleucine residue at sequence position 780 that aligns with the conserved methionine at position 918 of Vsscl and other insect **sodium channels**. Channels mutated to contain methionine at position 780 (1780M) exhibited enhanced sensitivity to cismethrin and larger decay constants for pyrethroid-modified channel states. In contrast, the **mutation** corresponding to M918Tin the Vsscl channel (1780T) profoundly decreased the cismethrin sensitivity of expressed channels. Insertion of the **mutation** corresponding to L1014F (L879F in rNav1.8) reduced the cismethrin sensitivity of channels having either isoleucine or methionine at position 780, whereas channels

containing the 1780T/L879F double **mutation** were insensitive to this insecticide. **Mutations** at Ile780 and Leu879 also modified the voltage dependence of rNav1.8 channels, but these effects were not related to changes. . . sensitivity. These results confirm the importance of residues in homology domain II as fundamental determinants of the pyrethroid sensitivity of **sodium channels**.

CT . . .
pharmacology
Ion Channel Gating: DE, drug effects
Ion Channel Gating: GE, genetics
Membrane Potentials: GE, genetics
Models, Biological
Oocytes
Phenotype
***Point Mutation**
*Pyrethrins: PD, pharmacology
Rats
Sodium Channels: DE, drug effects
***Sodium Channels: GE, genetics**
Tetrodotoxin: PD, pharmacology
Xenopus laevis

CN 0 (DNA, Complementary); 0 (Insecticides, Botanical); 0 (Pyrethrins); 0 (**Sodium Channels**)

L15 ANSWER 13 OF 27 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

TI Dysfunction of the Na+ channel alpha2 subunit gene **Nav1**.2 (SCN2A) leads to febrile and afebrile seizures in humans.

PY **2001**

AU Hirose, Shinichi [Reprint author]; Fukuma, Goryu [Reprint author]; Ito, Masatoshi; Nagafuji, Hiroshi; Sugawara, Takashi; Nagata, Keiichi; Kaneko, Sunao; Yamakawa, Kazuhiro; Mitsudome, Akihisa

TI Dysfunction of the Na+ channel alpha2 subunit gene **Nav1**.2 (SCN2A) leads to febrile and afebrile seizures in humans.

SO Epilepsia, (2001) Vol. 42, No. Supplement 7, pp. 19. print.
Meeting Info.: Annual Meeting of the American Epilepsy Society. Philadephia, PA, USA. November 30-December 05, 2001. American Epilepsy Society.
CODEN: EPILAK. ISSN: 0013-9580.

IT . . .

IT Diseases
generalized epilepsy with febrile seizure plus: nervous system disease, diagnosis, etiology, genetics

IT Chemicals & Biochemicals
genomic DNA; **sodium channel** alpha-2 subunit: expression; **sodium channel** alpha-2 subunit cDNA [**sodium channel** alpha-2 subunit complementary DNA]; sodium ion: influx

GEN human Na-v1.2 gene [human **sodium channel** alpha-2 subunit gene] (Hominidae): allele, exon, intron, **mutation**; human SCN2A gene [human **sodium channel** alpha-2 subunit gene] (Hominidae): allele, exon, intron, **mutation**; rat Na-v1.2 gene (Muridae): expression, **mutation**

L15 ANSWER 14 OF 27 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

TI Two novel **mutations** of the voltage-gated Na+ channel alpha1 subunit gene **Nav1**.1 (SCN1A) found in individuals with febrile seizures (FS) associated with afebrile partial seizures.

PY **2001**

AU Fukuma, Goryu [Reprint author]; Hirose, Shinichi [Reprint author]; Sugawara, Takashi; Ito, Masatoshi; Nagafuji, Hiroshi; Wada, Kazumaru;

Kaneko, Sunao; Yamakawa, Kazuhiro; Mitsudome, Akihisa
TI Two novel **mutations** of the voltage-gated Na+ channel alpha1 subunit gene **Nav1**.1 (SCN1A) found in individuals with febrile seizures (FS) associated with afebrile partial seizures.
SO Epilepsia, (2001) Vol. 42, No. Supplement 7, pp. 18-19. print.
Meeting Info.: Annual Meeting of the American Epilepsy Society. Philadephia, PA, USA. November 30-December 05, 2001. American Epilepsy Society.
CODEN: EPILAK. ISSN: 0013-9580.
IT . . .
plus: nervous system disease, diagnosis, genetics
IT Diseases
genetic abnormality: genetic disease
IT Chemicals & Biochemicals
genomic DNA; valine-1418; voltage-gated **sodium channel** alpha-1 subunit: transmembrane domain
GEN human NA-v1.1 gene [human voltage-gated **sodium channel** alpha-1 subunit gene] (Hominidae): exon, intron, **mutation**; human SCN1A gene [human voltage-gated **sodium channel** alpha-1 subunit gene] (Hominidae): exon, intron, **mutation**

L15 ANSWER 15 OF 27 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
TI Missense **mutations** of the voltage-gated **sodium channel** alphaI and alphaII subunit genes (**Nav1**.1 and **Nav1**.2) in patients with febrile and afebrile seizures.
PY **2001**
AU Sugawara, T. [Reprint author]; Ito, M.; Agarwala, K. L. [Reprint author]; Mazaki, E. [Reprint author]; Fukuma, G.; Mitsudome, A.; Nagafuji, H.; Kaneko, S.; Hirose, S.; Yamakawa, K. [Reprint author]
TI Missense **mutations** of the voltage-gated **sodium channel** alphaI and alphaII subunit genes (**Nav1**.1 and **Nav1**.2) in patients with febrile and afebrile seizures.
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 1468. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001.
ISSN: 0190-5295.
AB. . . febrile seizures (FS), is characterized by frequent episodes beyond 6 years of age (FS+) and various types of subsequent epilepsy. **Mutations** in betaI and alphaI-subunit genes of voltage-gated **sodium channels** have been associated with GEFS+1 and 2, respectively. Here we report three missense **mutations** of the gene encoding the **Nav1**.1 and another three **mutations** of **Nav1**.2 in patients with FS associated with afebrile seizures. Among **Nav1**.1 **mutations**, A1675V substitution in a transmembrane helix and V1418A in the pore-forming region are assumed to be responsible for the disease phenotype because of their co-segregation with disease phenotype and absence in normal controls. Among **mutations** of **Nav1**.2, R187W was not found in 224 alleles of unaffected individuals and was suggested to be responsible for the disease phenotype. This finding proposes **Nav1**.2 as a new entry of genes responsible for human epilepsy. Results of functional analyses of these **mutant** channels supporting this proposal will be presented in the accompanying paper (Nagata et al.).
IT . . .
nervous system disease, pathogenesis
IT Diseases
generalized epilepsy with febrile seizure: nervous system disease, pathogenesis
IT Chemicals & Biochemicals
voltage-gated **sodium channel** alpha-I subunit;

voltage-gated **sodium channel** alpha-II subunit
GEN human **Nav1**.1 gene (Hominidae): expression, **mutation**, voltage-gated **sodium channel** alpha-I subunit gene; human **Nav1**.2 gene (Hominidae): expression, **mutation**, voltage-gated **sodium channel** alpha-II subunit gene

L15 ANSWER 16 OF 27 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
TI Residue-specific effects on slow inactivation at V787 in D2-S6 of **Nav1**.4 **sodium channels**.
PY **2001**
AU O'Reilly, John P. [Reprint author]; Wang, Sho-Ya; Wang, Ging Kuo
TI Residue-specific effects on slow inactivation at V787 in D2-S6 of **Nav1**.4 **sodium channels**.
SO Biophysical Journal, (October, 2001) Vol. 81, No. 4, pp. 2100-2111. print. CODEN: BIOJAU. ISSN: 0006-3495.
AB Slow inactivation in voltage-gated **sodium channels** (NaChs) occurs in response to depolarizations of seconds to minutes and is thought to play an important role in regulating. . . NaCh slow inactivation, we substituted different amino acids at position V787 (valine) in D2-S6 of rat skeletal muscle NaCh mu1 (**Nav1**.4). Whole-cell recordings from transiently expressed NaChs in HEK cells were used to study and compare slow inactivation phenotypes between **mutants** and wild type. V787K (lysine substitution) showed a marked enhancement of slow inactivation. V787K enters the slow-inactivated state apprxeq100X faster. . . change in molecular conformation that is associated with the slow inactivation state. Our results suggest that the V787 position in **Nav1**.4 plays an important role in slow inactivation gating and that molecular rearrangement occurs at or near residue V787 in D2-S6. . .
IT . . . Concepts
Membranes (Cell Biology)
IT Parts, Structures, & Systems of Organisms
skeletal muscle: muscular system
IT Chemicals & Biochemicals
Na-v-1.4 **sodium channel**; amino acids; cysteine: modification; methanethiosulfonate ethylammonium; voltage-gated **sodium channels**

L15 ANSWER 17 OF 27 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
TI Nax channel is involved in control of salt intake behavior in CNS.
PY **2001**
AU Watanabe, E. [Reprint author]; Fujikawa, A.; Matsunaga, H.; Yasoshima, Y.; Sako, N.; Yamamoto, T.; Noda, M. [Reprint author]
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 393. print. Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001. ISSN: 0190-5295.
AB Nax (formerly known as **Nav2**/NaG) is a putative **sodium channel**, whose physiological role has long been an enigma. We generated Nax gene deficient mice by inserting the lacZ gene. Analysis. . . and organum vasculosum laminae terminalis compared with wild-type animals, suggesting a hyperactive state in the Nax-null mice. Consistently, the null **mutants** showed abnormal intakes of hypertonic saline. These findings suggest that the Nax channel plays an important role in the central. . .
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name

mouse: Nax-null, **mutant**, wild type
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
GEN mouse Nax gene (Muridae): expression, **mutation**; mouse c-fos gene (Muridae): expression; mouse lacZ gene (Muridae): expression

L15 ANSWER 18 OF 27 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
TI Dose-dependent modulation and suppression of **sodium channel** currents by **mutant** beta1 subunits associated with GEFS+1 epilepsy.
PY **2001**
AU Loukas, A. [Reprint author]; Kriegler, S.; Kazen-Gillespie, K. A.; Malhotra, J. D.; Koopmann, M. C.; Ragsdale, D. S. [Reprint author]; Isom, L. L.
TI Dose-dependent modulation and suppression of **sodium channel** currents by **mutant** beta1 subunits associated with GEFS+1 epilepsy.
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 117. print. Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001. ISSN: 0190-5295.
AB Generalized epilepsy with febrile seizures plus type 1 (GEFS+1) is caused by a cysteine to tryptophan **mutation** (C121W) in SCN1B. C121 is thought to play a critical role in disulfide bond formation in the extracellular Ig fold. . . expression levels, homophilic cell adhesion leading to ankyrin recruitment, and interactions with extracellular matrix molecules. Previous studies reported that this **mutation** in beta1 interferes with channel gating and may create a loss-of-function allelle. We found that C121Wbeta1 is expressed at the. . . does not participate in homophilic adhesion in Drosophila S2 cells. In contrast to previously reported results, coexpression of C121Wbeta1 with **Nav1**.2a in oocytes resulted in dose-dependent modulation of Na+ current. Maximal speeding of current time course by C121Wbeta1 required injection of 200-times more RNA than wild type beta1, suggesting that higher levels of expression of the **mutant** protein were required for full modulation of channel function. We also observed a large, dose-dependent suppression of whole cell currents with coinjection of C121Wbeta1 RNA, suggesting that the **mutant** subunit exerts a dominant negative effect on channel expression at the cell surface. Interestingly, C121Wbeta1 suppressed **Nav1**.2a amplitude even when coexpressed with wild type beta1, as would occur in an individual heterozygous for the disease allele.
IT . . .
System (Neural Coordination)
IT Diseases
generalized epilepsy with febrile seizures plus type 1: nervous system disease
IT Chemicals & Biochemicals
sodium channel beta-1 subunit: cysteine to tryptophan **mutation**
IT Miscellaneous Descriptors
channel gating; **sodium channel** currents: dose-dependent modulation, suppression; Meeting Abstract

L15 ANSWER 19 OF 27 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
TI Nax channel is involved in monitoring extracellular sodium concentration.
PY **2001**
AU Hiyama, T. Y. [Reprint author]; Watanabe, E. [Reprint author]; Yoshīda, S.; Noda, M. [Reprint author]

SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 393. print. Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001. ISSN: 0190-5295.

AB Nax (**Nav2**/NaG) channel has been classified as a subfamily of the voltage-gated **sodium channels**. However, physiological properties of the channel remains to be elucidated, since all the efforts to functionally express it in heterologous. . . to 170 mM, a marked increase of (Na+)i was observed in DRG neurons derived from wild-type mice but not from null-**mutant** mice. In order to further verify this finding, subfornical organ neurons, which are known to play an important role in. . .

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse: Nax null-**mutant**, animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

L15 ANSWER 20 OF 27 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN

TI Kinetic changes of voltage-gated **sodium channels** by a missense **mutation** of alpha II subunit gene **Nav1**.2 in a patient with febrile and afebrile seizures.

PY **2001**

AU Tsurubuchi, Y. [Reprint author]; Nagata, K. [Reprint author]; Sugawara, T. [Reprint author]; Imoto, K.; Noda, M.; Narahashi, T.; Nontal, M.; Hirose, S.; Yamakawa, K. [Reprint author]

TI Kinetic changes of voltage-gated **sodium channels** by a missense **mutation** of alpha II subunit gene **Nav1**.2 in a patient with febrile and afebrile seizures.

SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 117. print. Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001. ISSN: 0190-5295.

AB **Mutations** of **sodium channel** beta1-subunit and alpha-subunit type 1 (**Nav1**.1) genes have been reported to be responsible for generalized epilepsy with febrile seizures plus (GEFS+). In the accompanying paper (Sugawara et al.), we described **mutations** in a **sodium channel** alpha-subunit type 2 (**Nav1**.2) gene in patients with GEFS+. To examine whether the **mutations** of **Nav1**.2 gene affect Na+ channel function, we examined the electrophysiological properties of rat **Nav1**.2 channels, with or without corresponding **mutations**, expressed in HEK293 cells using the whole-cell patch clamp technique. Only the R187W **mutant** channel inactivated more slowly than wild-type as well as other **mutants** while the Na+ channel conductance was not affected. Prolonged residence in the open state of the R187W **mutant** channel may augment Na+ influx and thereby underlie the neuronal hyperexcitability that induces seizure activity. These findings strongly suggest the involvement of **Nav1**.2 in a human disease. We here propose the R187W **mutation** as the genetic defect responsible for febrile seizures associated with afebrile seizures.

IT . . .
seizures: nervous system disease
IT Diseases
generalized epilepsy with febrile seizures plus: nervous system disease
IT Chemicals & Biochemicals

voltage-gated **sodium channels**: kinetic changes

GEN human **Nav1**.2 gene [human **sodium channel** alpha II subunit gene] (Hominidae): missense **mutation**

L15 ANSWER 21 OF 27 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
TI Role of neutral residues in the voltage sensors of domains I and II in **sodium channel** activation.
PY **2001**
AU Bendahhou, S. [Reprint author]; Duclohier, H.; Cummins, T. R.; Leuchtag, H. R.; Waxman, S. G.; Ptacek, L. J.
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 117. print. Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001. ISSN: 0190-5295.
TI Role of neutral residues in the voltage sensors of domains I and II in **sodium channel** activation.
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 1, pp. 117. print. Meeting Info.: 31st Annual Meeting of the Society for Neuroscience. San Diego, California, USA. November 10-15, 2001. ISSN: 0190-5295.
AB Amino acid **mutations** in the voltage sensors S4 produce channel abnormalities, either at the activation or inactivation levels leading to severe channel dysfunction. . . forms of myotonia. We have shown that substitution of branched amino acid residues with unbranched residues, in DIII-S4, mainly altered **sodium channel** inactivation properties (Bendahhou et al., Biophys. J. 80:229a). These substitutions had similar effects to those seen when charged amino acids. . . voltage sensors were replaced with neutral residues. Now, we extend this study to other domains of the human skeletal muscle **sodium channel** (**Nav1**.4) in order to elucidate the role of the evenly spaced branched residues in the voltage sensors. Alanine-scanning mutagenesis was applied. . . in DI-S4 and DII-S4 (L224A, L227A, L674A, and F677A). Whole-cell patch clamp technique was used to monitor wild type and **mutant** currents in HEK293 cells. While **mutations** of the branched residues in DIII-S4 affected mainly channel inactivation parameters, **mutations** in DI and DII altered only the activation properties. The inactivation parameters remain unaffected with these **mutations**, more evidence that activation-inactivation coupling may be occurring only through the S4s of DIII and DIV. These results further support the notion of an asymmetric **sodium channel** functioning, each homologous domain underlying different aspects of channel gating.
IT . . .
IT Diseases
myotonia: muscle disease, nervous system disease
Myotonia (MeSH)
IT Diseases
periodic paralysis: nervous system disease
IT Chemicals & Biochemicals
sodium channel [**Nav1**.4]: activation; voltage sensor neutral residues

L15 ANSWER 22 OF 27 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation. on STN
TI **Sodium channel Nav1**.6 is localized at nodes of Ranvier, dendrites, and synapses.
PY **2000**
AU Caldwell, John H. [Reprint author]; Schaller, Kristin L.; Lasher, Robert S.; Peles, Elior; Levinson, S. Rock
SO Proceedings of the National Academy of Sciences of the United States of America, (May 9, 2000) Vol. 97, No. 10, pp. 5616-5620. print. CODEN: PNASA6. ISSN: 0027-8424.
TI **Sodium channel Nav1**.6 is localized at nodes of Ranvier, dendrites, and synapses.

SO Proceedings of the National Academy of Sciences of the United States of America, (May 9, 2000) Vol. 97, No. 10, pp. 5616-5620. print. CODEN: PNASA6. ISSN: 0027-8424.

AB Voltage-gated **sodium channels** perform critical roles for electrical signaling in the nervous system by generating action potentials in axons and in dendrites. At least 10 genes encode **sodium channels** in mammals, but specific physiological roles that distinguish each of these isoforms are not known. One possibility is that each. . . or is targeted to a specific domain of a neuron or muscle cell. Using affinity-purified isoform-specific antibodies, we find that **Nav1**.6 is highly concentrated at nodes of Ranvier of both sensory and motor axons in the peripheral nervous system and at nodes in the central nervous system. The specificity of this antibody was also demonstrated with the **Nav1**.6-deficient mouse **mutant** strain med, whose nodes were negative for **Nav1**.6 immunostaining. Both the intensity of labeling and the failure of other isoform-specific antibodies to label nodes suggest that **Nav1**.6 is the predominant channel type in this structure. In the central nervous system, **Nav1**.6 is localized in unmyelinated axons in the retina and cerebellum and is strongly expressed in dendrites of cortical pyramidal cells. . . and cerebellar Purkinje cells. Ultrastructural studies indicate that labeling in dendrites is both intracellular and on dendritic shaft membranes. Remarkably, **Nav1** .6 labeling was observed at both presynaptic and postsynaptic membranes in the cortex and cerebellum. Thus, a single **sodium channel** isoform is targeted to different neuronal domains and can influence both axonal conduction and synaptic responses.

IT . . .
nodes of Ranvier: nervous system; peripheral nervous system: nervous system; synapses: nervous system

IT Chemicals & Biochemicals
Na-v 1.6: localization, **sodium channel**, voltage-gated

L15 ANSWER 23 OF 27 USPATFULL on STN

TI Method of obtaining small conformationally rigid conopeptides

IN Olivera, Baldomero M., Salt Lake City, UT, United States
Hillyard, David R., Holiday, UT, United States
Myers, Richard A., Salt Lake City, UT, United States
Scott, Jamie K., Columbia, MO, United States
Smith, George P., Columbia, MO, United States

PI US 5885780 19990323 <--

GOVI This invention was made with government support under Contract No. N00014-88-K-0178 awarded by the Department of the **Navy** and under Contract No. GM-22737 awarded by the Department of Health and Human Services. The government has certain rights in. . .

DETD . . . inside the cylindrical coat 22 but containing no pIII protein. The pIII gene 24 has been modified by a frameshift **mutation** so that the pIII protein is not produced. In the absence of a frame restoring insert, the phage particles lack. . .

CLM What is claimed is:
14. A method according to claim 13 wherein said target protein is a **sodium channel** receptor.